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on behalf of the European Network Coordinating research on REnal Denervation (ENCOReD) Consortium

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## Experience at 11 European Expert Centers

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***Abstract***—Based on the SYMPLICITY studies and CE (Conformité Européenne) certification, renal denervation is currently applied as a novel treatment of resistant hypertension in Europe. However, information on the proportion of patients with resistant hypertension qualifying for renal denervation after a thorough work-up and treatment adjustment remains scarce. The aim of this study was to investigate the proportion of patients eligible for renal denervation and the reasons for noneligibility at 11 expert centers participating in the European Network COordinating Research on renal Denervation in treatment-resistant hypertension (ENCOReD). The analysis included 731 patients. Age averaged 61.6 years, office blood pressure at screening was 177/96 mm Hg, and the number of blood pressure–lowering drugs taken was 4.1. Specialists referred 75.6% of patients. The proportion of patients eligible for renal denervation according to the SYMPLICITY HTN-2 criteria and each center's criteria was 42.5% (95% confidence interval, 38.0%–47.0%) and 39.7% (36.2%–43.2%), respectively. The main reasons of noneligibility were normalization of blood pressure after treatment adjustment (46.9%), unsuitable renal arterial anatomy (17.0%), and previously undetected secondary causes of hypertension (11.1%). In conclusion, after careful screening and treatment adjustment at hypertension expert centers, only ≈40% of patients referred for renal denervation, mostly by specialists, were eligible for the procedure. The most frequent cause of ineligibility (approximately half of cases) was blood pressure normalization after treatment adjustment by a hypertension specialist. Our findings highlight that hypertension centers with a record in clinical experience and research should remain the gatekeepers before renal denervation is considered. (***Hypertension*****. 2014;63:1319-1325.)** ● **Online Data Supplement**

**Key Word:** Antihypertensive Agents ■ Hypertension Resistant to Conventional Therapy ■ Sympathetic Denervation

Depending on populations studied and applied methods and definitions, the prevalence of treatment-resistant hypertension varies from 3% to 30%.[1,2] The SYMPLICITY studies[3–5] demonstrated that in this indication catheter-based endovascular sympathetic renal denervation (RDN) by means of low-frequency energy is feasible. It entails a 25- to 30-mm Hg decrease in office systolic blood pressure, 84% of patients achieving a decrease in office systolic blood pressure of ≥10 mm Hg with a rate of procedural adverse events <5% assessed 6 months after RDN.[4] However, as reviewed

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*A list of all European Network Coordinating research on REnal Denervation (ENCOReD) consortium participants is given in the Appendix.

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elsewhere,[6,7] blood pressure decrease observed after RDN is highly variable[8] and probably much less than previously thought, especially when ambulatory blood pressure monitoring is used.[8–10] Furthermore, stenosis[11,12] and damage[13] of the renal arteries can occur after RDN, and the long-term effect of RDN on renal function is still unclear.[5,14,15] Hence, until more and better evidence is available, RDN should remain the last resort in patients with truly resistant hypertension.[6,7] Accordingly, several national and international consensus papers[16,17] have proposed guidelines for evaluation and management of patients with resistant hypertension before considering RDN. The proportion of patients with truly resistant hypertension eligible for RDN and the reasons of noneligibility after thorough screening and optimization of drug treatment in expert centers remain elusive. In this study, we reviewed the reasons for noneligibility at 11 hypertension expert centers performing RDN for treatment-resistant hypertension and collaborating within the European Network COordinating research on Renal Denervation (ENCOReD).[8]

## Methods

### Patients

We performed systematic reviews of the literature published elsewhere[6,7] and identified ENCOReD centers engaging in RDN. At the fourth ENCOReD network meeting, held in Leuven on April 26, 2013, all 12 centers involved in ENCOReD were invited and accepted to take part in this study. Eventually, 1 center was removed from the final analysis because not all information required for the present analysis could be retrieved from the local database. The 11 other contributing centers provided information on 731 consecutive patients referred for RDN. All patients underwent a center-specific 3- to 6-month diagnostic and therapeutic work-up. The eligibility criteria for RDN at the participating centers were similar to those of the SYMPLICITY studies with the following differences: (1) office systolic blood pressure should be ≥140 mm Hg (3 centers) or ≥160 mm Hg in patients without diabetes mellitus or ≥150 mm Hg in patients with diabetes mellitus (3 centers), or the 24-hour systolic blood pressure should be ≥130 mm Hg, irrespective of the level of office blood pressure (8 centers); (2) patients with white-coat–resistant hypertension were not eligible (8 centers); (3) evaluation of renal artery anatomy by computed tomography or MRI was mandatory (all centers); (4) patients with >2 renal arteries were eligible provided that the length and diameter of the arteries fulfilled the SYMPLICITY criteria (all centers); (5) the lower limit of the estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease formula was 30 mL/min per 1.73 $m^2$ (5 centers) or 45 mL/min per 1.73 $m^2$ (3 centers); in 1 center, patients were excluded if serum creatinine was >200 μmol/L and 2 centers did not set limits to eGFR; and (6) drug adherence was assessed according to electronic compliance monitoring (1 center), plasma dosage of drugs and their metabolites (1 center), pharmacy refill (1 center), witnessed drug intake (3 centers), or the Morisky adherence questionnaire (1 center).

Investigators completed a template data sheet for all these patients. It collected information on anthropometric characteristics of the referred patients, their office and ambulatory blood pressure, drug treatment at the first visit, eligibility for RDN according to the SYMPLICITY HTN-2 inclusion and exclusion criteria (E1)[4] and the centers' own assessment (E2), and reasons of noneligibility. The comprehensive list of noneligibility criteria included older age/frailty; morbid obesity; altered renal function; previous cholesterol emboli or diffuse atherosclerosis; white-coat–resistant hypertension (conventional blood pressure ≥140/90 mm Hg but daytime ambulatory blood pressure <135/85 mm Hg); renal artery stenosis; renal artery stenting; other anatomic reasons precluding RDN; primary aldosteronism; pheochromocytoma; other causes of secondary hypertension; blood pressure controlled or substantially improved after treatment adjustment, including or not low-dose (25–50 mg) spironolactone; poor drug adherence; and patient or referring physician's refusal. Furthermore, participants had the possibility to add other reasons as free text. For each patient considered noneligible by the center (E2), >1 reason of noneligibility could be provided.

### Statistical Methods

We used SAS software (SAS Institute, Cary, NC), version 9.3, for database management and statistical analysis. Continuous data are presented as mean±SD and categorical data as frequencies and percentages. We compared means and proportions by a large sample $z$ test and the $\chi^2$ statistic, respectively. We applied a κ statistic to assess agreement between diagnostic criteria. We applied stepwise logistic regression to search for variables associated with an increased likelihood of being eligible for RDN. $P$ values for independent variables to enter and stay the model were set at 0.15. The variables considered for entering into the models were sex, age, body mass index, baseline systolic blood pressure, eGFR, total number of drugs taken, a history of diabetes mellitus, coronary artery disease, stroke, and peripheral artery disease. Odds ratios express the independent increase in risks associated with a 1-SD increase in continuous covariables or a condition of interest (eg, sex). Significance was a 2-sided $P$ value of ≤0.05.

## Results

### Baseline Characteristics

Information was obtained on 731 subjects. Specialists referred 75.6% of patients (mostly cardiologists and nephrologists), and general practitioners referred 24.4% of patients. Baseline blood pressure, the frequency of comorbidities, drug treatment score, and drug classes (Table 1) were similar to those observed in SYMPLICITY HTN-2.[4] Notably, at the first visit to the referral center, 14.9% of patients had no drug inhibiting the renin–angiotensin system, 27.2% had no calcium antagonist, and 18.0% had no diuretic (Table 2; Figure S1 in the online-only Data Supplement). Furthermore, 21.5% were prescribed 2 or even 3 drugs inhibiting the renin–angiotensin system. The proportion of patients under spironolactone was low (26.0%) even in patients with eGFR ≥45 (28.1%) or ≥60 mL/min per 1.73 $m^2$ (27.0%). The proportion of patients who had taken spironolactone in the past was 20.9% (95% confidence interval [CI], 17.1%–24.7%), 22.4% (CI, 18.2%–26.6%), and 22.8% (CI, 18.1%–27.5%) in the whole group and in patients with eGFR ≥45 or ≥60 mL/min per 1.73 $m^2$, respectively.

### Eligibility Status

Fewer than half of patients were eligible for RDN, both according to the SYMPLICITY HTN-2 criteria (E1, 42.5%; CI, 38.0%–47.0%) and the centers' own judgment (E2, 39.7%; CI, 36.2%–43.2%), with substantial variability between centers (Table 3). In patients with apparently resistant hypertension (office systolic blood pressure ≥140 mm Hg, despite prescription of ≥3 antihypertensive drug classes; n=601) and in patients with office systolic blood pressure ≥160 mm Hg and eGFR ≥45 mL/min per 1.73 $m^2$ (n=433), the proportion of eligible patients was slightly higher (E1, 45.4% and E2, 40.1%; and E1, 60.2% and E2, 48.3%, respectively). Eligibility status was moderately consistent between E1 and E2 (κ coefficient of agreement, 0.49). As may be expected, the proportion of eligible patients was higher in the subset referred by specialists than in patients referred by general practitioners (E1, 47.0% versus 31.6%; $P$<0.001; and E2, 43.6% versus 27.5%; $P$<0.001).

**Table 1. Main Characteristics of Patients Referred for RDN According to Eligibility Status**

| Characteristics | All Patients n=731 | E2 Patients n=290 (39.7%) | Non-E2 Patients n=441 (60.3%) |
|---|---|---|---|
| Women, n (%) | 336 (46.0) | 122 (42.1) | 214 (48.5) |
| Age, y | 61.6±12.0 | 60.0±11.3 | 62.7±14.4* |
| White, n (%) | 701 (95.9) | 276 (95.2) | 425 (96.4) |
| Office systolic pressure, mm Hg | 176.7±27.2 | 183.8±27.6 | 172.1±25.9† |
| Office diastolic pressure, mm Hg | 96.2±16.8 | 100.9±17.1 | 93.2±16.0† |
| 24-h systolic pressure, mm Hg | 154.7±20.1 | 160.7±17.9 | 149.8±20.5† |
| 24-h diastolic pressure, mm Hg | 89.5±14.6 | 94.4±13.6 | 85.5±14.2† |
| No. of drug classes | 4.1±1.6 | 4.3±1.8 | 3.9±1.5* |
| Body mass index, kg/m$^2$ | 30.0±5.6 | 29.0±5.8 | 30.2±5.5 |
| Diabetes mellitus, n (%) | 184/668 (27.5) | 75/278 (27.0) | 109/390 (28.0) |
| Coronary artery disease, n (%) | 134/667 (20.1) | 54/277 (19.5) | 80/390 (20.5) |
| Stroke, n (%) | 44/457 (9.6) | 14/171 (8.2) | 30/286 (10.5) |
| Peripheral artery disease, n (%) | 83/665 (12.5) | 33/278 (11.9) | 50/387 (12.9) |
| eGFR classes, mL/min per 1.73 m$^2$ | 73.8±22.5 | 76.1±21.7 | 72.3±22.9‡ |
| | n=686 | n=275 | n=411 |
| <30 | 15 (2.2) | 2 (0.7) | 13 (3.2) |
| 30–45 | 64 (9.3) | 19 (6.9) | 45 (11.0) |
| ≥45 | 607 (88.5) | 254 (92.4) | 353 (85.9) |

Data are mean±SD or number of patients (%). E2 indicates patients eligible for renal denervation according to the centers' own criteria; eGFR, estimated glomerular filtration rate; non-E2, patients ineligible for renal denervation according to the centers' own criteria; and RDN, renal denervation.

Difference between E2 and non-E2 patients: *$P$<0.01, †$P$<0.001, ‡$P$<0.05. Difference in the eGFR classification between E2 and non-E2: $P$=0.017.

## Determinants of Eligibility

Compared with patients considered ineligible by the centers (non-E2), eligible patients (E2) were slightly but significantly younger, had a significantly higher office and ambulatory blood pressure, were taking more drug classes, and had a higher eGFR (Table 1). In a stepwise logistic regression model, age, baseline blood pressure, number of blood pressure–lowering drugs, eGFR, and body mass index were associated with the likelihood of eligibility for RDN. Eligibility for RDN was independently related with 1-SD increase in office systolic blood pressure (odds ratio [OR], 1.87; CI, 1.54–2.25; $P$<0.001), increase in the number of blood pressure–lowering drugs (OR, 1.31; CI, 1.09–1.57; $P$=0.004), and increase in eGFR (OR, 1.25; CI, 1.04–1.51; $P$=0.02), lower age (OR, 0.72; CI, 0.59–0.87; $P$=0.001), and lower body mass index (OR, 0.84; CI, 0.70–1.01; $P$=0.064).

Reasons for noneligibility with a frequency of ≥5% (Figures 1 and 2; Table S1) were (1) controlled or substantially improved blood pressure after treatment adjustment (46.9%), in 49.7% of cases using a regimen including low-dose spironolactone (25–50 mg/d); (2) anatomic reasons (17.0%, renal artery stenosis, history of renal stenting, or other anatomic reasons); (3) secondary hypertension (11.1%, most often primary aldosteronism but also including autonomic dysfunction and hypercortisolism); (4) decreased renal function (9.1%); (5) older age and frailty (7.9%); (6) white-coat–resistant hypertension (7.7%); and (7) poor drug adherence (7.7%).

A nonexhaustive list of other reasons of noneligibility encompassed morbid obesity (n=17); patient (n=10) or referring physician (n=3) refusing the procedure; diffuse atherosclerosis or previous cholesterol emboli (n=2); proteinuria (n=2); clear cell carcinoma/renal mass (n=2); subarachnoid hemorrhage (n=1) or unstable angina pectoris (n=2) before RDN; nephrotic proteinuria because of light chain disease (n=1); bilateral fibromuscular dysplasia (n=1); hydronephrosis (n=1); primary hyperparathyroidism (n=1); chronic autoimmune disease (n=1); psychiatric illness (n=1); or alcohol abuse (n=1). Of note, in 26.3% of patients deemed ineligible, ≥2 reasons of noneligibility were present.

## Discussion

In this multicenter cohort, only ≈40% of patients referred for RDN, mostly by specialists, were eligible for the procedure, according to the SYMPLICITY HTN-2 criteria, as well as according to the centers' own judgment. These data confirm at the European level the results obtained by Verloop et al[18] in a Dutch single-center cohort, also included in ENCOReD. The proportion of less complex, standard patients with resistant hypertension in whom RDN seems both feasible and justified is probably still an order of magnitude lower (7.5% in patients with resistant hypertension hospitalized for hypertension in a French third referral center; 2.6% according to a recent US chart review)[2,19] and might further decrease if all patients would be assessed for drug adherence[20] or would have received maximal and optimized drug treatment, including low-dose spironolactone whenever possible.[19]

As in the Dutch study,[18] patients found to be ineligible for RDN in our current study were older and had lower office and ambulatory blood pressures and medication scores. Although the proportion of patients eligible for RDN was of the same

**Table 2. Drug Treatment of Patients Referred for Renal Denervation at the First Visit Before Treatment Adjustment**

| Drug Treatment | No. of Patients |
|---|---|
| Total number | 692 |
| Antihypertensive drug classes, n | 4.1±1.6 |
| Inhibitors of the renin–angiotensin system | |
| Total | 589 (85.1) |
| Converting enzyme inhibitors (n=418) | 180 (43.1) |
| Angiotensin receptor blockers (n=418) | 223 (53.4) |
| Aliskiren (n=418) | 60 (14.4) |
| ≥2 inhibitors of the renin system (n=418) | 90 (21.5) |
| Calcium channel blockers | 504 (72.8) |
| Diuretics | |
| Total | 568 (82.0) |
| Thiazide (n=418) | 279 (66.8) |
| Loop diuretic (n=418) | 120 (28.7) |
| Spironolactone | 180 (26.0) |
| β-Blockers | 498 (71.9) |
| α-Blockers | 141 (20.4) |
| Centrally acting drugs | 175 (25.3) |
| Vasodilators | 42 (6.1) |

The Utrecht center did not have detailed information on file on the subclassification of renin system inhibitors or diuretics.

order of magnitude in the Dutch and our study (33.1% versus 39.7%), the leading causes of ineligibility substantially differed. In particular, whereas in the Dutch cohort,[18] successful treatment adjustment excluded only 12% of the referred patients from RDN, in our European cohort, treatment optimization allowed to control blood pressure in ≈50% of noneligible patients, despite the fact that most patients were referred because blood pressure control was considered impossible to achieve, often after years of unsuccessful attempts.

In half of cases (Figure 1), treatment adjustment involved prescription of low-dose spironolactone (25–50 mg/d). Additional changes might have included prescription of other drug classes, optimization of the dose of diuretics and stepped care combination of diuretics acting at different nephron segments (sequential nephron blockade),[21] use of more potent or long-acting drugs, and use of double or triple fixed drug combinations to increase drug adherence. One might also hypothesize that consultation in a specialized center and the perspective of use of RDN, an invasive and still exceptional procedure, might have convinced a proportion of patients to adhere more strictly to their drug treatment, which may explain substantial blood pressure improvements observed in some patients despite minimal treatment changes.

Once more, the proportion of patients amenable to blood pressure control might be an underestimation because not all investigators attempted to obtain maximal treatment in all patients. One may expect that the proportion is higher in unselected cohorts of patients with resistant hypertension. These findings are at odds with the frequent belief, held by some investigators and disseminated by the device industry that, for patients with resistant hypertension, per definition, no reasonable further pharmaceutical options are available.[22] They highlight the importance of skilful treatment adjustment and the important role of hypertension tertiary referral centers as gatekeepers before RDN is considered.

The effect of treatment optimization should also be interpreted in the light of the drug regimen at the first referral visit, which was neither maximal nor optimal in a substantial proportion of patients. In line with the data published by Hanselin et al,[23] the association of 2 or even 3 renin–angiotensin system blockers, a less efficacious and potentially harmful drug combination,[24,25] was used in 22% of patients, whereas diuretics (82%) and, notably, calcium antagonists (73%) were still underused. In particular, low-dose spironolactone, a recommended drug in patients with resistant hypertension[26,27] was prescribed in only 26% of patients (Table 2), even in a subset with normal renal function, which is much higher than in the US database explored by Hanselin et al[23] (5.9%) and slightly better than in 2 other cohorts of patients referred in

**Table 3. Proportion of Referred Patients Eligible for RDN After Thorough Work-Up and Treatment Adjustment**

| Center Name | No. of Patients | Eligible According to SYMPLICITY HTN-2 Criteria (E1) Number (%), 95% Confidence Interval | Eligible According to Centers' Own Criteria (E2) Number (%), 95% Confidence Interval |
|---|---|---|---|
| Lausanne | 53 | 19 (35.9), 23.0–48.8 | 14 (26.4), 14.5–38.3 |
| Geneva | 32 | 16 (50.0), 32.7–67.3 | 12 (37.5), 20.7–54.3 |
| Hannover | 91 | 44 (48.4), 38.1–58.7 | 48 (52.8), 42.5–63.1 |
| Prague | 18 | 14 (77.8), 58.6–97.0 | 4 (22.2), 3.0–41.4 |
| Oslo | 18 | 10 (55.6), 32.6–78.6 | 6 (33.3), 11.5–55.1 |
| Stockholm | 21 | 15 (71.4), 52.1–90.7 | 17 (81.0), 64.2–97.8 |
| Odense | 64 | 7 (10.9), 3.3–18.5 | 7 (10.9), 3.3–18.5 |
| Glasgow | 52 | 33 (64.5), 51.5–77.5 | 25 (48.1), 34.5–61.7 |
| Brussels | 91 | 31 (34.1), 24.2–43.8 | 33 (36.3), 26.4–46.2 |
| Utrecht | 274 | … | 119 (43.4), 37.5–49.3 |
| Krakow | 17 | 5 (29.4), 7.7–51.1 | 5 (29.4), 7.7–51.1 |
| All centers | 731 | 194/457 (42.5), 38.0–47.1 | 290/731 (39.7), 36.2–43.2 |

RDN indicates renal denervation.

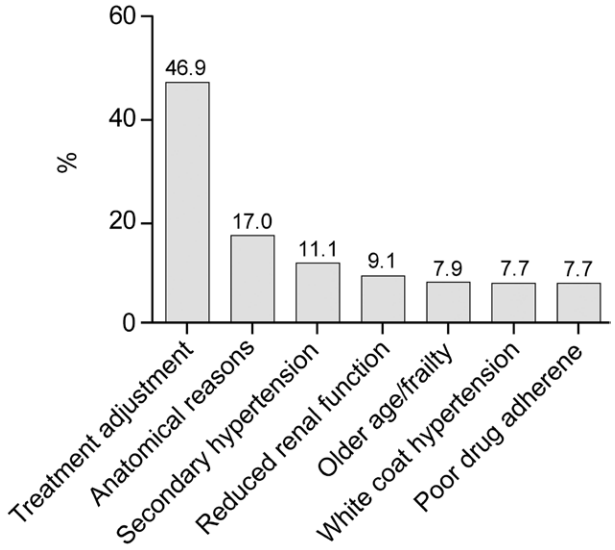


**Figure 1.** Reasons of noneligibility for renal denervation after thorough work-up and treatment optimization in 11 expert hypertension centers. For each patient, several reasons of noneligibility could be applicable (see Figure 2). Only reasons with a frequency of ≥5% were plotted.

hypertension expert centers (24%)[18,19] but clearly remains below expectations. Indeed, although spironolactone was tried in the past but stopped at the time of referral in the expert center in ≈20% additional patients, likely because of poor efficacy or drug intolerance, half of patients were never exposed to a mineralocorticoid receptor antagonist.

The frequency of other causes of ineligibility for RDN deserves specific comments. Compared with Simplicity HTN-2,[4] the proportion of patients excluded for anatomic reasons was similar (17% versus 24%), despite the fact that, in our cohort, patients with multiple renal arteries were considered as eligible, provided the length and diameter of the main renal arteries were ≥20 mm and 4 mm, respectively.[4] Although the low frequency of white-coat–resistant hypertension (8% versus 38% in the Spanish registry on ambulatory blood pressure monitoring)[28] likely reflects preselection by referring physicians, the prevalence of secondary hypertension was similar to that reported in other studies (12%),[18,29] despite the fact that most patients were referred by specialists.

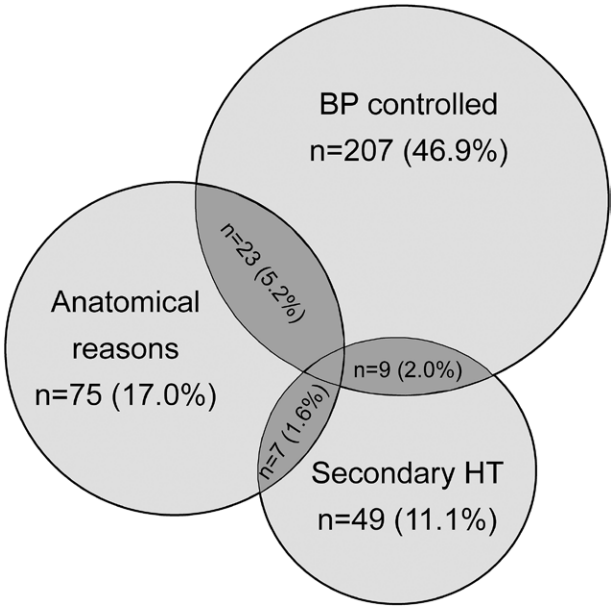


**Figure 2.** Main reasons of noneligibility of patients with resistant hypertension screened for renal denervation. BP indicates blood pressure; and HT, hypertension.

This study has to be interpreted within the context of its limitations, the most important being the heterogeneity in referral and eligibility criteria, screening, selection, and treatment algorithms between the different centers. Second, the exact nature and dosage of drugs used, proportion of single-pill versus fixed-dose combinations, and the precise strategy used by each center for treatment adjustment were not available. Finally, drug adherence was not evaluated according to standardized methods in all centers. However, our study, the largest conducted thus far, has the advantage of involving multiple centers, thus providing a more representative overview of screening for RDN in European hypertension centers. It also generated information on the effect of treatment adjustment in resistant hypertension. Furthermore, the limitations mentioned previously might only have led to an underestimation of the proportion of ineligible patients, and in particular of patients amenable to blood pressure target after drug treatment optimization, and thus are unlikely to affect the key messages of this study. These are (1) only a minority of patients referred for RDN are eligible for the technique; (2) the most frequent cause of ineligibility (46.9%) was blood pressure normalization after treatment adjustment in the expert center; and (3) in more than half of patients successfully controlled by drug treatment optimization, low-dose spironolactone was part of the therapeutic arsenal.

## Perspectives

In view of the persistent uncertainties on the safety and efficacy of RDN—further emphasized by the recent announcement of the failure of SYMPLICITY HTN-3[30] to reach its primary efficacy end point (http://www.tctmd.com/show.aspx?id=123265)—difficult to treat patients and patients with resistant hypertension should be thoroughly evaluated in an expert hypertension center before RDN is considered (http://www.bcs.com/pages/news_full.asp?NewsID=19792021). More generally, the availability of RDN as last-line treatment for patients with resistant hypertension is a unique opportunity to revisit the diagnostic and therapeutic algorithms of resistant hypertension and to increase awareness about the best diagnostic and therapeutic strategies in this small subset of patients with hypertension. Finally, although current eligibility criteria are mostly based on SYMPLICITY HTN-2[4] and medical common sense, future works should focus on the identification of patients most likely to benefit from RDN, with the lowest probability of adverse events or complications. In particular, identification of predictive factors of blood pressure response post-RDN is a priority. In this respect, our first study on the efficacy of RDN within the ENCOReD network suggested a higher probability of blood pressure response in patients with established cardiovascular disease.[8] Conversely, higher baseline serum creatinine was associated with lower probability of blood pressure improvement after RDN.[8]

Although preliminary, these results may pave the way toward identification of responder and nonresponder profiles in currently planned or ongoing randomized controlled studies.

## Appendix

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## Novelty and Significance

### What Is New?

- In a multicenter European cohort of 731 patients referred for renal denervation to leading hypertension centers, only ≈40% qualified.
- The most frequent cause of ineligibility (46.9%) was blood pressure normalization after treatment adjustment in the expert center, removing the indication for renal denervation.
- Other reasons of ineligibility included incompatible renal artery anatomy (17.0%) and secondary hypertension (11.1%).

### What Is Relevant?

- The diagnosis of resistant hypertension requires out-of-the-office blood pressure monitoring.
- Management of resistant hypertension by combining antihypertensive drugs in optimal doses and combinations is substandard in Europe, highlighting the need for continuing education of physicians.
- Renal denervation remains a last-resort approach that should only be applied at expert hypertension centers in a context of clinical research. The failure of SYMPLICITY HTN-3 to reach its primary end point of efficacy supports this contention.
- Hypertension expert centers should be the gatekeepers to give patients access to renal denervation.

### Summary

This study showed that in 731 patients representative for clinical practice at 11 European hypertension expert centers (mean age, 61.6 years; office blood pressure, 177/96 mm Hg, number of drugs, 4.1), only 39.7% of patients referred for renal denervation qualified. The main reasons of noneligibility were normalization of blood pressure after treatment adjustment (46.9%), incompatible renal artery anatomy (17.0%), and previously undetected secondary hypertension (11.1%).

HYPERTENSION

# Eligibility for Renal Denervation: Experience at 11 European Expert Centers

Eligibility for Renal Denervation

**ONLINE SUPPLEMENT**

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**Table S1** Reasons of non-eligibility for renal denervation after thorough work-up and treatment adaptation in the centers (E2) (starts)

| Center name | Non-E2 patients | Blood pressure controlled after treatment adjustment | | | Anatomical reasons | | | |
|---|---|---|---|---|---|---|---|---|
| | | Spirolactone given | Spirolactone not given | Total | Renal artery stenosis | Renal stenting | Other | Total |
| Lausanne | 39 | 8 (20.5) | 8 (20.5) | 16 (41.0) | 2 (5.1) | 1 (2.6) | 4 (10.3) | 5 (12.8) |
| Geneva | 20 | 4 (20.0) | 4 (20.0) | 8 (40.0) | 0 | 0 | 0 | 0 |
| Hannover | 43 | 22 (51.2) | 17 (39.5) | 39 (90.7) | 1 (2.3) | 0 | 0 | 1 (2.3) |
| Prague | 14 | 1 (7.1) | 7 (50.0) | 8 (57.1) | 0 | 0 | 0 | 0 |
| Oslo | 12 | 0 | 1 (8.3) | 1 (8.3) | 0 | 0 | 1 (8.3) | 1 (8.3) |
| Stockholm | 4 | 0 | 2 (50.0) | 2 (50.0) | 0 | 1 (25.0) | 0 | 1 (25.0) |
| Odense | 57 | 17 (29.8) | 22 (38.6) | 39 (68.4) | 4 (7.0) | 0 | 3 (5.3) | 7 (12.3) |
| Glasgow | 27 | 3 (11.1) | 2 (7.4) | 5 (18.5) | 2 (7.7) | 0 | 10 (37.0) | 12 (44.4) |
| Brussels | 58 | 20 (34.5) | 12 (20.7) | 32 (55.2) | 4 (6.9) | 5 (8.6) | 10 (17.2) | 17 (29.3) |
| Utrecht | 155 | NA | NA | 54 (34.8) | 14 (9.0) | 4 (2.6) | 5 (3.2) | 23 (14.8) |
| Krakow | 12 | 1 (8.3) | 2 (16.7) | 3 (25.0) | 3 (25.0) | 0 | 5 (41.7) | 8 (66.7) |
| 11 centers | 441 | 76 | 77 | 207 (46.9) | 30 (6.8) | 11 (2.5) | 38 (8.6) | 75 (17.0) |

NA indicates information not available. Data are number of patients (%). The table includes reasons for non-eligibility with a frequency of at least 5%. Numbers do not add up, because patients could have more than one reason making them ineligible.

**Table S1** Reasons of non-eligibility for renal denervation after thorough work-up and treatment adaptation in the centers (E2) (continued)

| Center name | Secondary hypertension | | | Reduced renal function | Older age/frailty | White-coat hypertension | Poor drug adherence |
|---|---|---|---|---|---|---|---|
| | Primary aldosteronism | Other cause | Total | | | | |
| Lausanne | 7 (18.0) | 1 (2.6) | 8 (20.5) | 9 (23.1) | 12 (30.8) | 1 (2.6) | 3 (12.5) |
| Geneva | 0 | 0 | 0 | 2 (10.0) | 1 (5.0) | 6 (30.0) | 3 (15.0) |
| Hannover | 0 | 0 | 0 | 0 | 2 (4.7) | 0 | 3 (7.0) |
| Prague | 4 (28.6) | 0 | 4 (28.6) | 0 | 0 | 7 (50.0) | 3 (21.4) |
| Oslo | 0 | 0 | 0 | 0 | 0 | 5 (41.7) | 0 |
| Stockholm | 0 | 1 (25.0) | 1 (25.0) | 1 (25.0) | 0 | 0 | 1 (25.0) |
| Odense | 1 (1.8) | 0 | 1 (1.8) | 13 (22.8) | 9 (15.9) | 6 (10.5) | 4 (7.0) |
| Glasgow | 0 | 3 (11.1) | 3 (11.1) | 2 (7.4) | 3 (11.1) | 2 (7.4) | 2 (7.4) |
| Brussels | 0 | 0 | 0 | 12 (20.7) | 8 (13.8) | 6 (10.3) | 0 |
| Utrecht | 25 (16.1) | 4 (2.6) | 29 (18.7) | NA | NA | NA | 9 (6%) |
| Krakow | 0 | 3 (25.0) | 3 (25.0) | 1 (8.3) | 0 | 1 (8.3) | 6 (50%) |
| 11 centers | 37 (8.4) | 12 (2.7) | 49 (11.1) | 40 (9.1) | 35 (7.9) | 34 (7.7) | 34 (7.7) |

Data are number of patients (%). Reasons of non-eligibility declared in < 5% of cases are not indicated. NA: not available.

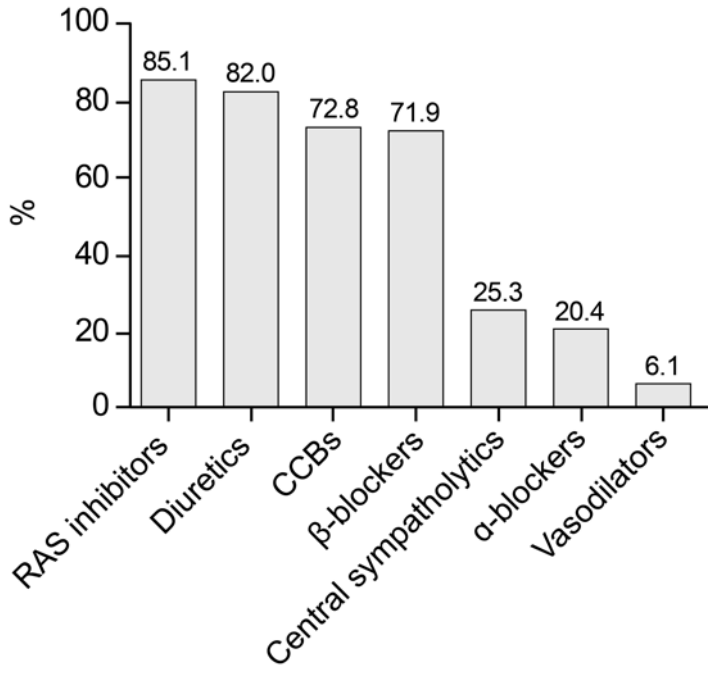


**Figure S1** Proportion of prescribed antihypertensive drug classes in patients referred for renal denervation, before treatment adjustment in the 11 expert centers. RAS inhibitors refer to renin angiotensin inhibitors (includes angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and the direct renin inhibitor aliskiren). CCBs refers to calcium channel blockers.